REMARKS

Claim Rejections: 35 U.S.C. § 112

The Examiner has rejected claims 1-3 and 10 under 35 U.S.C.§ 112, ¶ 1, on grounds that the specification, while being enabled for TGF-β RII/Fc fusion proteins of SEQ ID NOS:8 and 9, allegedly reasonably does not provide enablement for all TGF-β R fusion proteins. In support of this proposition, the Examiner cites in general terms the enablement factors enumerated in *In re Wands, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988)* that may be applied *ex parte* to determine enablement. These factors are: (1) the quantity of experimentation necessary (2) the amount of direction or guidance presented (3) the presence or absence of working examples (4) the nature of the invention (5) the state of the prior art (6) the relative skill of those in the art (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Per *Wands,* these factors are illustrative, not mandatory; what is relevant depends on the facts.

Per the Examiner, the Applicants have not provided sufficient guidance for one of ordinary skill in the art to make and use the fusion proteins of claims 1-3 and 10. The Examiner notes that claims 1, 2 and 10, although requiring that the claimed fusion proteins competitively inhibit the binding of TGF- β to a TGF- β receptor, are not limited with respect to the type of TGF-β R protein claimed, and further that claims 1, 2 and 10 are not limited to a specific fusion partner. *Massague (Ann. Rev. Biochem. 1998, vol. 67, pp. 753-791)* ("*Massague*") is said by the Examiner to disclose that TGF-β receptors have different properties. The Examiner cites *Massague* in support of the proposition that the type I receptor cannot bind TGF- β receptors independently of the type II receptor, and that TGF- β2 binds the type II receptor weakly in the absence of the auxiliary receptor betaglycan.

Based on this interpretation of *Massague*, the Examiner concludes that those of ordinary skill in the art could not reasonably use all proteins within the scope of claims 1-

3 and 10 to bind to all forms of TGF-.β with sufficient affinity to inhibit those forms of TGF- β from binding to other receptors. Further, the Examiner asserts that there is no structural guidance as to what insertions or deletions need to be made to obtain sufficient binding or to define the variants that fall within the scope of claims 1-3 and 10.

These reasons offered by the Examiner to support her finding that claims 1-3 and 10 are not enabled are not supportable. Each of the Claims, including claims 1-3 and 10, is fully enabled, for the reasons that follow.

The specification of the instant application sets forth in great detail the variants that fall within the scope of claims 1-3 and 10, and provides clear and specific guidance to those of skill in the art as to how those variants can be made and used in accordance with the invention. At page 27, lines 1-5, the Applicants provide detailed direction and guidance that enabled those of skill in the art as of the effective filing date to make and use the invention of the Claims, including claims 1-3 and 10. There, the Applicants disclose that the claimed invention encompasses:

"[v]arious bioequivalent protein and amino acid analogs [that] have an amino acid sequence corresponding to all or all part of the extracellular region of a native TGF-beta receptor (e.g., SEQ ID NO:8 or 9) or amino acid sequences substantially similar …at least 60% homologous to the sequences of SEQ ID NO: 8 or 9 and which are biologically active in that they bind to TGF-beta ligand."

Detailed exemplary procedures, including reference to four articles, are cited at page 27, lines 10-17, to illustrate how to ascertain, through signal transduction activity, whether a protein satisfies the competitive inhibition limitation of the Claims, including claims 1-3 and 10.

Additionally, at page 28 of the application, lines 9-13, the Applicants again specify that natural, recombinant, or synthetic proteins of the Claims, including claims 1-3 and 10:

"include an amino acid sequence at least 60%, 80%, 90%, 95%, 98%, or 99% homologous to an amino acid sequence from SEQ ID NOS: 8 or 9. The polypeptide is at least 5, 10, 20, 50, 100, or 150 amino acids in length and includes at least 5, preferably at least 10, most preferably at least 20, most preferably at least 50, 100, or 150 contiguous amino acids from SEQ NOS: 8 or 9."

Thus, the specification of the instant application provides specific detailed guidance to those of skill in the art with respect to the structure of proteins within the scope of all of the Claims, including claims 1-3 and 10. The requisite homology of the amino acid sequences of proteins within the scope of all of the Claims, including claims 1-3 and 10, is provided. Further, the specification of the instant application provides specific detailed guidance to those of skill in the art on how to determine which of the proteins competitively inhibit binding of TGF-beta to a TGF-beta receptor. Signal transduction techniques well-known to those of ordinary skill in the art are highlighted in this regard.

The breadth of enablement of the specification of the instant application is commensurate in scope with all of the Claims, including claims 1-3 and 10, as the quantity of experimentation necessary to determine both the claimed fusion protein amino acid sequence and ability to competitively inhibit binding of TGF-beta to a TGF-beta receptor is not undue, given the aforementioned detailed teaching regarding amino acid sequence homology and inhibitory activity potential. *Fiers v. Revel, 25 U.S.P.Q.2d 1601 (Fed. Cir. 1993)*(claims enabled where there was detailed teaching in specification of method of obtaining DNA encoding protein).

With the disclosure of the instant application, those of skill in the art as of the effective filing date could have, without undue experimentation, naturally derived, recombinantly expressed, or synthetically made amino acid sequence at least 60%, 80%, 90%, 95%, 98%, or 99% homologous to an amino acid sequence from SEQ ID NOS:8 or 9 of the application. *See* accompanying *Declaration of Philip Gotwals,Ph. D. ¶ 2*

("Declaration"), which the Applicants respectfully request the Examiner to consider along with this Response. With the disclosure of the instant application, and without undue experimentation, those of ordinary skill in the art could have applied the signal transduction techniques disclosed in the application to determine if proteins comprising such sequences inhibited binding of TGF-beta to a TGF-beta receptor. *Id. Cf. Ajinomoto Co., Inc. v. Archer-Daniels Midland Co., 56 U.S.P.Q.2d 1332 (Fed. Cir. 2000)*(claimed method to genetically modify bacterium to produce amino acid enabled as it used conventional and well-known techniques).

The fact that the scope of claims 1-3 and 10 encompasses "proteins not yet known in the art", *July 30, 2002 Office Action, page 3*, does not render those claims nonenabled. *Ajinomoto, supra.* The key inquiry is whether those of skill in the art could identify, make, and test the proteins of claims 1-3 and 10, whether or not they were known at the time of filing. Ample support for the fact that they could have done so has been provided herein. *See also In Re Wands, supra* (improper to reject generic claims to monoclonal antibodies (mab's) for lack of enablement on grounds that only a certain percentage of hybridomas were proven to fall within the claims and exemplified mab's came from only a few fusions; it was within the skill of the art to screen mab's to determine if they fell within the scope of claims).

Further, the specification of the instant application provides clear and particular guidance as to the nature of the fusion partners used in proteins of claims 1-3 and 10. The application discloses at page 26, lines 18-20, that "[s]pecifically, the second protein may be the constant region of an immunoglobulin (preferably IgG, most preferably IgG1) or may be a portion thereof such as the hinge, C_H2 or C_H3." Those of ordinary skill in the art as of the effective filing date could have, with the disclosure of the instant application and without undue experimentation, identified and isolated such immunoglobulin regions or portions thereof without undue experimentation. *Declaration, ¶ 3.*

In light of the foregoing, it is apparent that the cited excerpts from *Massague* do not in any way suggest that claims 1-3 and 10 are nonenabled. *Massague* does describe the variety in ligand binding of TGF- β receptors I and II, but provides no basis to suggest that TGF-β fusion proteins comprising amino acid sequences of the homology previously described and constant regions of an immunoglobulin (preferably IgG, most preferably IgG1) or a portion thereof such as the hinge, C_H2 or C_H3, will not inhibit binding of TGF- β to a TGF-β receptor as defined in the application. *Declaration, ¶ 4.* Significantly, the *Lin* patent, which was cited by the Examiner in support of her obviousness rejection and which is discussed further hereinafter, also notes that a common functionality of TGF- β I and II receptors has been suggested (column 7, lines 14-17). *Lin* thereby provides further evidence of the impropriety of the outstanding enablement rejections.

The specification of the instant application teaches those of ordinary skill in the art how to make and use the invention as broadly as it is claimed. It is well-settled that the scope of generic claims can encompass more than specific species disclosed in the specification. *In Re Wands, supra. See also Mycogen Plant Science, Inc. v. Monsanto Co., 58 U.S.P.Q.2d 1891 (Fed. Cir.), reh'g denied, 59 U.S.P.Q.2d 1852 (Fed. Cir. 2001)*(single example could possibly support generic claims where specification included codon usage tables, recommendations on the preferred level of homology, and means for calculating deviation of the frequency of preferred codon usage).

Example 2 of the instant application illustrates in vitro binding of TGF- βRII:Fc to TGF- β. Example 3 of the instant application discloses the inhibition of the anti-proliferative effect of TGF- β1 by administration of TGF- βRII:Fc. As discussed, the specification, e.g., at page 26, lines 18-20, and at page 28, lines 9-13, describes in detail the structure of the claimed fusion proteins. At page 27, lines 10-17, the specification provides several techniques that may be employed to determine the requisite competitive inhibition limitation of claims 1-3 and 10. This is more than adequate support to teach

those of ordinary skill in the art how to make and use the invention of each of the pending claims. *In Re Wands, supra.*

Claim Rejections: 35 U.S.C. § 103

The Examiner has rejected the Claims under 35 U.S.C.§ 103(a) ("Section 103(a)") as being unpatentable as obvious in light of U.S. Patent No. 6,046,157 ("*Lin*") in view of U.S. Patent No. 5,605,690 ("*Jacobs*").

The Examiner concedes that *Lin* does not teach Fc fusion proteins. The Examiner further concedes that *Jacobs* does not teach TGF- βRII fusion proteins; *Jacobs* describes fusion proteins for soluble TNFα receptors. In the absence of any reference suggesting that *Lin* and *Jacobs* could some how be combined to yield the TGF- βR fusion proteins of the Claims, the Examiner merely argues that since *Lin* describes use of soluble TGF-βRII receptors to lower TGF- β levels, and *Jacobs* describes the use "in an analogous system" of TNFα fusion proteins to lower TNFα, one of ordinary skill in the art would have been motivated to combine these references to yield the invention of the Claims. This rejection is improper for the following reasons.

Pursuant to Section 103(a), a patent may not be obtained though the invention is not identically disclosed or described as set forth in Section 102 if the differences between the subject matter sought to be patented and the prior art are such that the invention as a whole would have been obvious at the time the invention was made to one of ordinary skill in the art to which said subject matter pertains. Subjective factual inquiries relating to the scope and content of the prior art, the level of ordinary skill in the art, and the differences between the prior art and the claimed invention must be considered in determining obviousness. *Hybritech, Inc. v. Monoclonal Antibodies, Inc, 231 U.S.P.Q. 81 (Fed. Cir.1986), cert den., 480 U.S. 947 (1987).* Objective factors relating to commercial success, long-felt need, failure of others, and unexpected results must also be considered. *Id.*

If the alleged obviousness of a claimed invention is based on a combination of references, there must be a rigorous showing of a clear and particular suggestion, teaching, or motivation to combine the references relied upon. *In Re Dembiczak, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999).* Such evidence may come from the references themselves, the knowledge of those skilled in the art, or from the nature of the problem to be solved. While this showing may come from the prior art, as filtered through the knowledge of one skilled in the art, *Brown and Williamson Tobacco Corp., Inc. v. Philip Morris Inc., 56 U.S.P.Q. 2d 1456 (Fed. Cir. 2000)*, it is still subject to the rigorous requirement that the combination not be motivated by impermissible hindsight. *In Re Dembiczak, supra.* Further, there must be a particular showing that one of ordinary skill in the art would have believed there was a reasonable likelihood of success that the suggested combination of references would work to yield the claimed invention. *Brown and Williamson Tobacco Corp, supra.*

Here, the Examiner has failed completely to establish a rigorous, particular showing that *Lin* and *Jacobs* would be combined to yield the invention of the Claims.

By the Examiner's own admission, *Lin* lacks any teaching of fusion proteins. *Lin* simply describes the DNA sequences encoding TGF- β II and III receptors and the expression and characterization of encoded products. *Lin* states that TGF- β II and III receptors encoded by the receptor genes of *Lin's* invention can be used as both agonists and antagonists to alter the effect of TGF- β *in vivo*. (*Lin*, column 7, lines 63-67; column 8, lines 1-7).

Jacobs describes TNFR/Fc fusion proteins comprising a single molecule of soluble TNFR linked to a single chain of Fc derived from human IgG1. There is no suggestion in *Jacobs* that TNFR are in any way "analogous" to TGF-βR. The DNA sequences and related compositions of *Jacobs* are wholly distinct from those of the Claims. *Declaration, ¶ 5.*

On these facts, one of ordinary skill in the art had no particular basis to combine *Lin* and *Jacobs* and no belief that there was a reasonable likelihood of success that the suggested combination of references would work to yield the claimed invention. *In Re Duel, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995)*, is instructive in this regard. *Duel* found that even where the prior art disclosed an amino acid sequence, the DNA encoding such sequence was not necessarily obvious. Per *Duel*, given the redundancy of the genetic code, there must be a particular showing that both leads to the claimed DNA and that indicates that it should be prepared.

The Examiner cannot point to any particular showing in *Lin* or *Jacobs* to prepare TGF-βR fusion proteins comprising: (1) "[v]arious bioequivalent protein and amino acid analogs [that] have an amino acid sequence corresponding to all or all part of the extracellular region of a native TGF-beta receptor (e.g., SEQ ID NO:8 or 9) or amino acid sequences substantially similar …[and] at least 60% homologous to the sequences of SEQ ID NO:8 or 9 and which are biologically active in that they bind to TGF-beta ligand"; and (2) the constant region of an immunoglobulin (preferably IgG, most preferably IgG1) or a portion thereof such as the hinge, C_H2 or C_H3.

Given the Examiner's position that the enablement for all TGF-β R fusion proteins is suspect in light of asserted differences in the behavior in different TGF-β R, it is incongruous for her to maintain that those of ordinary skill in the art would look to an entirely different receptor class, pick fusion proteins that are comprised of completely different components from those of the Claims, and deduce from the fact that TGF-β R were known antagonists and agonists that TGF-β R fusion proteins of the Claims could not only be made, but would prove active in inhibiting the binding of TGF-β to TGF-β receptors. Such reasoning necessarily resorts to impermissible hindsight. *In Re Dembiczak, supra.*

In light of all of the foregoing, it is respectfully maintained that each of the Claims are, like claim 5, patentable and in a condition for allowance and that the Examiner should withdraw all of her outstanding grounds for rejection. Accordingly, Applicants respectfully request that claims 1-7 and 10 be passed to issue.

Respectfully submitted,

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Version Showing Mark-ups

In the Specification:

On page 30, lines 11-18, please amend the paragraph as follows:

Like most mammalian genes, mammalian TGF-beta receptors are presumably encoded by multi-exon genes. Alternative mRNA constructs which can be attributed to different mRNA splicing events following transcriptions, and which share large regions of identify or similarity with the cDNAs claimed herein may also be used. [The vector containing the TGF-beta RII:fC cDNA clone, was used to express and purify soluble TGF-beta RII:Fc. Plasmid which expresses the fusion protein has been deposited with the American Type culture Collection, 12301 Parklawn Drive, Rockville, Md. 20852, U.S.A. (Accessions No. _____) under the name _____.] A plasmid expressing the TGF-beta Type II Recepor has been deposited with the American Type Culture Collection (ATCC), P.O. Box 1549, Manassas, VA 20108 USA), on November 12, 1997, by a third party and has an ATCC number of 209455. Other materials necessary to make a TGF-beta Type II Receptor fusion protein are also available in the public domain to those of ordinary skill in the art.